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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,519	SIDRANSKY ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,15 and 19-24* is/are pending in the application.

4a) Of the above claim(s) *20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12, 15,19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/23/2010 has been entered.

2. It is noted that the response to arguments and the amended claim sets are from 9/21/2009.

3. Claims 12, 15, 19-24 are pending. Claims 1-11, 13-14, 16-17 have been cancelled.

4. Claims 20-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/15/2006.

5. The rejections are set forth below for claims 12, 15, and 19. Response to arguments follows.

6. This action is Nonfinal.

Claim Rejections - 35 USC § 112/2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 12, 15, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 15, and 19 are unclear over the steps presented in Claim 12. Step a of claim 12 requires contacting primers to permit extension of a sequence complementary to a polynucleotide encoding exon 1 and exon 2. Step b requires the amplification of that extension and by contacting the extension products with an oligonucleotides that binds with sequences from a human 5' ALT gene. However, it is not clear that the extension product of step 1 includes such a gene as it only requires extension of a sequence encoding exon 1 and exon 2. Step c requires determining the presence of an amplification product that comprises 5' ALT alternative p16 transcript devoid of exon 1, however, the first two steps require an extension produce that encodes exon 1. As such it is not clear which sequences are required for detection.

Claim Rejections - 35 USC § 112/ Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention

8. Claims 12, 15, and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claim 12 is drawn to a method of detecting a cell proliferative disorder, comprising contacting a sample with RNA primers in exon 1 and exon 2 of the human p16 gene, amplifying the resulting extension product with a oligonucleotide which binds to a 5' ALT gene and determining the presence of a truncated p16 gene product with a homozygous deletion of exon 1, comprising detecting a first amplification product containing exon 2 of the p16 gene in the absence of identifying a second amplification product containing exon 1 of the p16 gene, wherein the presence of the truncated p16 gene product is associated with a cell proliferative disorder and wherein the cell proliferative disorder is lung or head and neck cancer. Claim 15 defines the sample. Claim 19 is defines the amplification reaction.

Therefore the claims encompass a method for detecting and correlating the absence of exon 1 of the p16 gene with lung or head and neck cancer in any sample type.

Nature of the Invention

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification

The specification asserts that the p16 gene has been identified as a region having homozygous deletions in many tumors and that the 5' ALT is shown to be about 30 kb upstream for p16 (p. 5 lines 6-9). Therefore it is unclear how to amplify the extension of exon 1 and 2 by using oligonucleotides that binds within the 5' ALT gene.

The claims are drawn to the detection of lung or head and neck cancer by detection the presence of a truncated p16 gene (e.g. the homozygous deletion of exon 1).

The specification asserts a method for detecting a cell proliferative disorder comprising contacting a cellular compound with a reagent which detects an alteration in p16 (p. 41 last paragraph). The specification asserts that the gene encoding the tumor suppressor p16 has been found to be deleted in certain cancers (p. 43 last paragraph). The instant specification asserts a method of detecting the presence or absence of all or particular regions of the human chromosome 9p21 (p. 44 1st paragraph).

Working Examples

Example 1 part 1: The specification asserts cells from head and neck cancer cell lines, lung cancer cell lines, pancreatic adenocarcinomas cell lines were extracted (p. 47 last paragraph).

Example 1 part 2 and 3: The specification asserts fragments of exon 1, 2, and 3 were amplified (p. 48 and 49). Example 4: The specification asserts the complete p16 and p16-5'ALT cDNA was amplified by RT-PCT (p. 57 1st full paragraph). The specification asserts that immunopreciptation was performed in which anti-p16 antibodies which recognize either the C-terminus or the N-terminus (p. 57 1st full paragraph). The specification asserts that the N-terminal antibody was not recognized indicating that the product lacked the N-terminal exon 1 coding sequence (p. 57 1st full paragraph).

Example 6: Table 1 presents 5' CpG island methylation related to allelic status and sequence analysis of the p16 in the cell lines. The p16 sequence indicates the majority of the primary human cancers, including head and neck and lung cancer, have the wild-type p16 sequence (p. 61). This indicates p16 with exon 1 present (wild type) would be observed in primary human cancers, therefore it is unpredictable to make an association of a mutant p16 gene (absent of exon 1) with cancers. Table 1 seems to indicate that NSCLC, SCLC, HNSCC had LOH of 9p21, however, the table is not clear because it also indicates that these tumors comprise the wild type p16 gene. Therefore the Table is unclear with regard to rather it is showing that these tumors have a homozygous deletion of exon 1 or the presence of exon 1.

Example 8: The example asserts that none of the methylated cells lines of NSCLC, SCLC, and HNSCC expressed p16 (p. 63 1st full paragraph). However, this is not sufficient guidance for enablement purposes because the art (Zhang et al.) teach that observation in cell lines are not directly correlative to tumor samples.

Example 11: The specification asserts Exon 1 of p16 lies in a CpG island which is unmethylated in normal tissue (p. 67 1st full paragraph). Table 2 shows inactivation of p16 in cell lines and primary tumors (p. 69). Table 2 discloses that in cell lines only breast and renal cancer have homozygous deleted p16 exon1 genes (p. 69). Table 2 discloses that none of the primary tumors which include samples from breast, colon adenoma, and colon cancer have homozygous deleted p16 (p. 69). Therefore the specification discloses that in many samples such as primary tumors and some cell lines there is no correlation of cell proliferative disorder and the absence of exon 1 in the p16 gene product. This example does not discuss the cancer types the claims are currently amended and therefore does not provide guidance for the association of a homozygous deletion of exon 1 with detection of lung or head and neck cancer.

The unpredictability of the art and the state of the prior art

Zhang et al. (Cancer Research 1994 Vol. 54 p. 5050) teaches detection of homozygous deletions of the p16 gene in 68 primary head and neck squamous cell carcinomas and 9 head and neck cell carcinoma cell lines (Abstract). Zhang et al. found that none of the primary tumors showed homozygous deletions of p16 (abstract). Zhang et al. teaches that p16 may play a role in tumorigenesis in some head and neck

squamous cell carcinomas but it probably occurs more frequently in cell lines as a result to adaptation to cell culture (abstract). Therefore the art teaches that a correlation in cell lines is cannot be directly extrapolated to tumors in a patient.

Washimi et al. (Cancer Research 1995 Vol. 55 p. 514) teaches that the homozygous deletion of p16 was only observed in non-small cell lung cancer carriers and not in all lung cancer carriers (Abstract). Therefore the art teaches that not all types of lung cancer are correlative to homozygous deletion of p16.

Okamoto (Cancer Research 1995 Vol. 55 p. 1448) discloses the examination of p16 in primary lung cancer and metastatic lung cancers (abstract). Okamoto et al. teaches that alterations of the p16 gene were detected in 6 of the 22 metastatic non small cell lung cancers, but non were detected in 25 primary NSCLCs, 15 primary small cell lung cancers, or 9 metastatic sclcs (abstract). Okamoto et al. asserts that therefore p16 is a late event in NSCLC carcinogenesis (abstract). In contrast to Washimi et al., Okamoto et al. did not find a correlation in all non small cell lung cancers. As such, even in the art, the correlation between deletion of exon 1 and lung cancer is not predictable.

Quantity of Experimentation

The quantity of experimentation in this area would be extremely large since there is significant number of parameters that would have to be studied. To practice the invention as broadly as it is claimed, the skilled artisan would have to determine the correlation of the deletion of exon 1 in the p16 gene with any lung or head and neck cancer wherein the art teaches that such associations are unpredictable.

Further the skilled artisan would need to perform undue experimentation to detect lung or head and neck cancer because both the art and the instant specification teach that deletion of exon 1 of p16 is not predictably detectable in all tumor or cell line types.

To use the invention as presented would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

Thus the applicants have not provided sufficient guidance to enable a skilled artisan to make the claimed invention in a manner reasonably correlated with the claimed method of detection of lung or head and neck cancer. The skilled artisan would have to perform undue experimentation to determine correlation of the absence of exon 1 of the p16 gene because the art teaches that such correlations are unpredictable.

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the negative teachings in the art, and the lack of guidance provided in the specification balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The reply traverses the rejection. A summary of the arguments in the reply and response to arguments is presented below.

It is noted that this full enablement is based upon the teaching in the specification only of cell lines and that art of record which teaches that cell line determination is not directly correlative to detection in human patients and the teaching of Woshimi et al. and Okamoto et al. who found different correlations in different types of lung or head and neck cancer. Further, the applicant has not provided any secondary considerations showing the predictably of association of the claimed product with any lung or head and neck cancer.

(A) The reply traverses the conclusions in the previous office action (p. 5 5/21/2009) and asserts that the examiner's conclusion fails to consider the basis of the present invention which is that the exon 1 coding region can be lost via alternative splicing of p16 gene transcripts (p. 6 1st paragraph).

This argument has been fully reviewed but has not been found persuasive.

The claims are drawn to a correlation of the presence of the truncated p16 gene product with a homozygous deletion of exon 1 with lung or head and neck cancer. The claims are not drawn to detection of the exon 1 coding region which can be lost via alternative splicing of p16 gene transcript, but to the correlation of the homozygous deletion to lung or head and neck cancer. As stated in the last office action (5/21/2009) the instant specification has not provided such support that in any sample there is correlation weighed against the art which teaches that such correlations are unpredictable.

(B) The reply asserts that that although the examiner cites Zhang et al. which teaches that none of the primary head and neck squamous cell carcinomas homozygous deletions of p16, that the invention shows that the methods used in Zhang may contribute to an underestimation of inactivation of p16 in tissue samples (p. 6 last paragraph).

This argument has been fully reviewed but has not been found persuasive.

The reply points to the specification on pages 74 to 75 to support that the invention used by Zhang et al. may contribute to an underestimation of inactivation of p16. The specification at these cited pages assert that consistent observations of homozygous deletion of p16 in primary tumors are difficult to detect by contamination by normal cells. The specification asserts that detection of aberrant DNA methylation of the p16 gene is not limited by the problem. However, the claims are towards contacting a sample comprising RNA and detecting the presence of a truncated p16 gene product. The claims are not limited to detection of methylation. Zhang et al. teaches that none of the head and neck squamous cell carcinomas showed homozygous deletions of p16 (abstract). Zhang et al. further teaches that although p16 may play a role in tumorigenesis in some head and neck squamous cell carcinomas, it probably occurs more frequently in cell lines as a result of adaptation to cell culture. Therefore the passages pointed out by the reply are drawn to methylation steps which are not present in the instant claim set and therefore do not overcome the unpredictably shown by Zhang et al. towards detection of homozygous deletions of p16.

(C) The reply asserts that although the examiner cites Okamoto et al. as supporting the assertion of a lack of correlation between homozygous deletion of p16 and lung cancer, the applicant note that the present inventor cites Okamoto as supporting the importance of p16 abnormalities in lung cancer (p. 7 1st and 2nd paragraph).

This argument has been fully reviewed but has not been found persuasive.

The cited passage of the instant specification asserts that in brain tumors and lung carcinomas, the later stage tumors have been reported to have higher rates of homozygous deletion of p16 suggested that p16 abnormalities may be a late progression event. This cited passage goes towards the support of the enablement, because the instant specification discloses that homozygous deletions of p16 might be only observable in late stage lung cancer. Further the cited reference states that p16 deletion is a late event in NSCLC carcinogenesis and that there is no association in other types of lung cancers (abstract). As such Okamoto et al. shows that there is not correlation between deletion of exon 1 and lung cancer.

(D) The reply asserts that none of these references disclose or suggest a 5'ALT alternative transcript of p16 as a means of inactivating p16 (p. 7 2nd paragraph). The reply asserts that thus the correlations that the authors cited may or may not have found are not relevant to the instant method of detecting a cell proliferative disorder by detecting the presence of a 5'ALT alternative p16 transcript devoid of the p16 exon 1 coding sequence (p. 7 2nd paragraph).

This argument has been fully reviewed but has not been found persuasive.

The claims are drawn to a correlation of the presence of the truncated p16 gene product with a homozygous deletion of exon 1 with lung or head and neck cancer. The claims are not drawn to only inactivating p16 gene by 5'ALT alternative transcript of p16. The cited references of Zhang, Washimi et al, and Okamoto et al., clearly teach that correlations of the homozygous deletion of p16 and lung and head and neck cancer are

dependent on the sample detected. The art discloses that associations observed in cell lines are different than those observed in tumor samples (Zhang et al.). Further as pointed out by the instant specification Okamoto teaches that these alterations are found only in lave event NSCLC carcinogenesis. As such the art discloses the unpredictably in the art with regard to the association of the deletion of a region of the p16 gene and lung or head and neck cancer.

(E) The reply asserts that the specification provides a correlation between p16 methylation and 5'ALT alternative p16 transcripts and cancer (p. 7 last paragraph). The reply points to example 6 asserting that the methylation status of the 5'CpG island of the p16 gene in a number of cancer cell lines (p. 7 last paragraph). The reply asserts that the 5'CpG island of the p16 gene is fully methylated in a number of cancer cell lines and primary cancers, but is unmethylated in all normal tissues (p. 7 last paragraph). The reply asserts that the specification provides RTPCR of total RNA in 8 tumor cell limes (without homozygous deletion) confirmed the presence of both alternative transcripts (p15ALT and p16ALT) (p. 7 last paragraph).

This argument has been fully reviewed but has not been found persuasive.

The reply points to example 6 in the instant specification for support for the correlation of the deletion of a region of the p16 gene and lung or head and neck cancer. It is noted that Example 6 is drawn to methylation status, as discussed above; the claims are not limited to methylation status.

The instant specification on p. 56-57 (as cited in the reply) states "RTPCR of total RNA from eight tumor cell lines (without homozygous deletion of this region) confirmed the presence of both alternative transcripts (p15ALT and p16ALT)". This citation from the specification does not support the enablement of the claims because as discussed on p. 5-6 of the last office action the instant specification provides conflicting assertions of these associations. As discussed on p. 5 of the last office action the specification asserts that the p16 sequence indicates the majority of the primary human cancers, including head and neck and lung cancer have the wild-type p16 sequence (p. 61). As such these cancers would not have the homozygous mutant p16 gene. Further, the art, as discussed above, teaches that these associations are sample specific. The art teaches that associations in cell lines are not correlative to tumors (see Zhang et al.). The art teaches that associated observed in late event NSCLC are not observed in early stages (see Okamoto et al.). Therefore the 35 USC 112/Enablemeent made in the last office action is maintained.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday - Friday 9AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Katherine Salmon/
Examiner, Art Unit 1634